

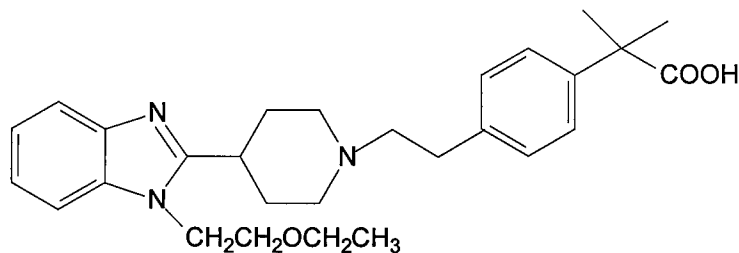
## AMENDMENT(S) TO THE SPECIFICATION

In the title of the application, please amend as follows:

Polymorph of 4-[2-[4-[1-(2-ethoxyethyl)-1H-~~benzimidazole~~ benzimidazole-2-yl]-1-piperidinyl]ethyl]- $\alpha$ -dimethyl-benzenecetic acid

Please replace the paragraph beginning at page 1, line 6, with the following rewritten paragraph:

The invention refers to a new polymorphous crystalline form of 4-[2-[4-[1-(2-ethoxyethyl)-1H-~~benzimidazole~~ benzimidazole-2-yl]-1-piperidinyl]ethyl]- $\alpha$ -dimethyl-benzenecetic acid (herein referred to as “bilastine”) of formula (I).



(I)

**Please replace the paragraph beginning at page 1, line 17, with the following rewritten paragraph:**

U.S. patent number 5,877,187 confers the rights to bilastine, a preparation with antihistaminic properties without sedative or cardiovascular effects. This patent also concerns a procedure to prepare bilastine and the use of this preparation to treat allergic reactions in mammals but it does not include or suggest the possible existence of polymorphic forms of this compound. To prepare pharmaceutical compositions containing bilastine for their administration in mammals and especially in man, in accordance with international health authority specifications, bilastine must be manufactured in the most stable crystalline form possible, especially in a form that has constant physical properties.

**Please replace the paragraph beginning at page 2, line 9, with the following rewritten paragraph:**

We have found that bilastine can exist in three different crystalline polymorphic forms, each with different physical properties.

**Please replace the paragraph beginning at page 2, line 12, with the following rewritten paragraph:**

The invention refers to a pure crystalline form of polymorph 1 of bilastine, characterised by X-ray ~~chromatographic~~ crystallographic analysis, with approximate crystal parameters as follows:

Crystallographic system	Monoclinical
Spatial group	P2 (1)/c
Crystal size	0.56 x 0.45 x 0.24 mm
Cell dimension	a=23.38 (5) A angstrom $\alpha = 90^\circ$ b=8.829 (17) A $\beta = 90^\circ$ c=12.59 (2) A $\gamma = 90^\circ$
Volume	2600 A <sup>3</sup>
Z, calculated density	4, 1.184 mg/m <sup>3</sup>

**Please replace the paragraph beginning at page 2, line 25, with the following rewritten paragraph:**

The crystalline polymorph 1 of bilastine is also characterised by its infrared absorption spectrum in potassium bromide tablet that has the following characteristic absorption bands, expressed in reciprocal centimeters;

3430 (s)\*; 3057 (w)\*; 2970 (s); 2929 (s); 2883 (m)\*; 2857 (m); 2797 (w); 1667 (m); 1614 (m); 1567 (w); 1509 (s); 1481 (m); 1459 (vs)\*; 1431 (m); 1378 (w); 1346 (m); 1326 (m); 1288 (w); 1254 (m); 1199 (w); 1157 (w); 1121 (vs); 1045 (w); 1020 (w); 1010 (w); 991 (w); 973 (w); 945 (w); 829 (w); 742 (s); 723 (w); 630 (w), \* where (w) = weak intensity, (m) = medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 1 represents the infrared spectrum of the crystalline polymorph 1 of the bilastine in a potassium bromide tablet recorded in a Fourier Perkin Elmer Spectrum One ~~transformer~~ FTIR spectrophotometer.

**Please replace the brief description of the figures beginning at page 3, line 13, with the following rewritten paragraphs:**

Figure 1 shows a typical infrared absorption spectrum in potassium bromide of polymorph 1. (Vertical axis: Transmission (%); Horizontal axis: ~~Bandnumber~~ Wavenumber (cm<sup>-1</sup>)).

Figure 2 shows a typical infrared absorption spectrum in potassium bromide of polymorph 2. (Vertical axis: Transmission (%); Horizontal axis: ~~Bandnumber~~ Wavenumber (cm<sup>-1</sup>)).

Figure 3 shows a typical infrared absorption spectrum in potassium bromide of polymorph 3. (Vertical axis: Transmission (%); Horizontal axis: ~~Bandnumber~~ Wavenumber (cm<sup>-1</sup>)).

**Please replace the paragraph beginning on page 3, at line 27, with the following rewritten paragraph:**

We have found that bilastine can exist in three clearly different polymorphic forms called ~~polymorph~~ polymorph 1, polymorph 2 and polymorph 3.

**Please replace the paragraph beginning at page 4, at line 1, with the following rewritten paragraph:**

The procedure described in US patent no. 5,877,187 generates a mixture of polymorphs 2 and 3. We have discovered experimental conditions and specific solvents to produce clearly different polymeric forms of bilastine. The crystalline polymorph 1 of pure bilastine is prepared according to the procedures of this invention. The polymorphic forms 1 and 2 are stable. Polymorph 3 is not very stable and is difficult to obtain in the pure form. Both polymorph 2 and polymorph 3 are converted into polymorph 1 ~~for the purposes~~ by the procedures of this invention.

**Please replace the paragraph beginning at page 4, line 10, with the following rewritten paragraph:**

Polymorph 1 of bilastine has a melting point of 200.3°C. Polymorph 2 has a melting point of 205.2°C. Polymorph 3 has a melting point of 197.0°C.

**Please replace the paragraph beginning at page 4, line 13, with the following rewritten paragraph:**

The crystalline polymorphic form 1 of bilastine is also characterised by its infrared absorption spectrum in potassium bromide that has the following characteristic absorption bands, expressed in reciprocal centimetres:

3430 (s)\*; 3057 (w)\*; 2970 (s); 2929 (s); 2883 (m)\*; 2857 (m); 2797 (w); 1667 (m); 1614 (m); 1567 (w); 1509 (s); 1481 (m); 1459 (vs)\*; 1431 (m); 1378 (w); 1346 (m); 1326 (m); 1288 (w); 1254 (m); 1199 (w); 1157 (w); 1121 (vs); 1045 (w); 1020 (w); 1010 (w); 991 (w); 973 (w); 945 (w); 829 (w); 742 (s); 723 (w); 630 (w), \* where (w) = weak intensity, (m) = medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 1 represents the infrared spectrum of the crystalline polymorph 1 of the bilastine in a potassium bromide tablet recorded in a ~~Fourier Perkin Elmer Spectrum One transformer~~ FTIR spectrophotometer.

**Please replace the paragraph beginning at page 4, line 27, with the following rewritten paragraph:**

The crystalline polymorphic form 2 of bilastine is also characterised by its infrared absorption spectrum in potassium that has the following characteristic absorption bands, expressed in reciprocal centimetres:

3429 (s)\*; 3053 (w)\*; 2970 (s)\*; 2932 (s); 2868 (s); 2804 (w); 1699 (m); 1614 (m)\*; 1567 (m); 1508 (s); 1461 (vs)\*; 1381 (m); 1351 (s); 1331 (m); 1255 (m); 1201 (w); 1156 (m); 1121 (vs); 1048 (w); 995 (w); 823 (w); 767 (w); 744 (s); 724 (w); 630 (w), \* where (w) = weak intensity, (m) = medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 2 represents the infrared spectrum of the crystalline polymorph 2 of the bilastine in a potassium bromide tablet recorded in a ~~Fourier~~ Perkin Elmer Spectrum One ~~transformer~~ FTIR spectrophotometer.

**Please replace the paragraph beginning at page 5, line 11, with the following rewritten paragraph:**

The crystalline polymorphic form 3 of bilastine is also characterised by its infrared absorption spectrum in potassium bromide that has the following characteristic absorption bands, expressed in reciprocal centimeters:

3430 (s)\*; 3053 (w)\*; 2970 (s); 2932 (s); 2868 (s); 2804 (w); 1291 (w); 1708 (m)\*; 1614 (m); 1568 (m); 1508 (s); 1461 (vs)\*; 1380 (m); 1351 (m); 1330 (m); 1271 (m); 1255 (M); 1201 (w); 1156 (m); 1121 (vs); 1048 (w); 995 (w); 823 (M); 767 (w); 744 (s); 724 (w); 630 (w), \* where (w) = weak intensity, (m) = medium intensity, (s) = strong intensity, (vs) = very strong intensity. Figure 3 represents the infrared spectrum of the crystalline polymorph 3 of the bilastine in a potassium bromide tablet recorded in a ~~Fourier~~ Perkin Elmer Spectrum One ~~transformer~~ FTIR spectrophotometer.

**Please replace the paragraph beginning at page 5, line 24, with the following rewritten paragraph:**

We have discovered that, ~~in~~ under selected experimental conditions, the mixture of the polymorphic forms 2 and 3, obtained according to US patent no. 5,877,187, is surprisingly transformed into polymorph 1. We have also discovered that polymorph 1 of bilastine is very stable and is not transformed into any of the other polymorphs 2 and 3. Similarly, in the same

experimental conditions, the pure polymorphic form 2 of bilastine is surprisingly transformed into the pure polymorphic form 1. Polymorphic form 3, which is the most unstable, undergoes the same transformation ~~in~~ under the same conditions.

**Please replace the paragraph beginning at page 6, line 4, with the following rewritten paragraph:**

Polymorph 1 of bilastine is a very stable polymorph at room temperature and is, therefore, very useful as an active ingredient of a pharmaceutical preparation. Polymorph 1 is also stable when stored at temperatures above room temperature.

**Please replace the paragraph beginning at page 6, line 9, with the following rewritten paragraph:**

The polymeric crystalline form 1 of bilastine is characterised by the following data of its X-ray crystallographic analysis as a monocrystal, with crystal parameters of approximately the following values:

Crystallographic system	Monoclinical	
Spatial group	P2 (1)/c	
Crystal size	0.56 x 0.45 x 0.24 mm	
Cell dimension	a=23.38 (5) Å angstrom $\alpha = 90^\circ$	
	b=8.829 (17) Å	$\beta = 90^\circ$
	c=12.59 (2) Å	$\gamma = 90^\circ$
Volume	2600 Å <sup>3</sup>	
Z, calculated density	4, 1.184 mg/m <sup>3</sup>	

**Please replace the paragraph beginning at page 6, line 22, with the following rewritten paragraph:**

During the development of polymorph 1 of bilastine for pharmaceutical preparations, elaborated according to correct manufacturing procedures, we have discovered that crystallization of bilastine (prepared according to the description given in US patent no5,877,187) of from short

chained alcohols, preferably isopropyl alcohol and n-butanol and its mixtures thereof, leads to generation of the pure polymeric form 1 of bilastine with a high yield. Crystallization ~~of~~ from acetone, dimethylsulphoxide, dimethylformamide, acetonitrile, and tetrahydrofurane or its mixtures thereof also lead to generation of polymorph 1, although with lower yields. It is, therefore, preferable to use the former solvents.

**Please replace the paragraph beginning on page 7, line 4, with the following rewritten paragraph:**

The infrared spectrum of polymorph 1 of bilastine in potassium bromide is characterised by the following bands, absent from polymorphs 2 and 3:

Wavelength Wavenumber (cm<sup>-1</sup>)

3057

2929

2883

2857

2797

1667

1481

1431

1346

1326

1288

973

945

829

**Please replace the paragraph beginning on page 7, line 23, with the following rewritten paragraph:**

Figure 1 shows the complete infrared spectrum of polymorph 1 of bilastine in potassium bromide, recorded with a ~~Fourier~~ Perkin Elmer Spectrum One ~~transformer~~ spectrophotometer.

**Please replace the paragraph beginning on page 8, line 1, with the following rewritten paragraph:**

Pharmaceutical preparations of this invention can contain, as well as an effective quantity of polymorph 1 of bilastine as an active ingredient as an antiallergic or antihistaminic agent, several pharmaceutically acceptable excipients that can be solid or liquid. The solid pharmaceutical preparations include powders, tablets, dispersible granules, capsules, ~~stamps~~ cachets and suppositories. A solid excipient can be one of several substances that act as diluents, aromatising agents, agglutinants or disintegrating agents and an encapsulation material. The powders and tablets preferentially contain from approximately 5 to approximately 20 per cent of the active ingredient. Appropriate solid excipients are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, waxes with low melting point, cocoa butter and similar products. The term "preparations" includes the formulation of the active ingredient with an excipient for encapsulation to produce a capsule in which the active ingredient (with or without other excipients) is surrounded with the excipient by an encapsulation material. Tablets, powders, ~~stamps~~ cachets and capsules can be used as suitable forms for oral administration. The active ingredient can also be incorporated into a chewing gum that can contain sweeteners, flavorings and colorings as appropriate.

**Please replace the paragraph beginning at page 8, line 22, with the following rewritten paragraph:**

To prepare suppositories, a compound with a low melting point, such as a mixture of fatty acid glycerides or cocoa butter, is melted and the active ingredient is mixed well and homogeneously dispersed in the mixture with agitation. The homogeneous melted mixture is placed in the appropriate moulds and left to cool until it solidifies.

**Please replace the paragraph beginning at page 8, line 28, with the following rewritten paragraph:**

Liquid preparations include suspensions, ~~lotions~~ solutions and emulsions. An example of these corresponds to aqueous suspensions that can be made by mixing the finely divided active ingredient in water with suspension agents. Aqueous solutions can be prepared by placing the



active ingredient in water and adding suitable coloring agents, aromas, stabilising agents, sweeteners, solubilising and thickening agents as appropriate.

**Please replace the paragraph beginning at page 9, line 6, with the following rewritten paragraph:**

Also, topical preparations are considered for nasal, ophthalmic and dermal use. Appropriate formulae for nasal administration can correspond to solutions or suspensions. Ophthalmic formulae can be ~~lotions~~ solutions, suspensions or ointments. Dermal preparations can be ~~lotions~~ solutions, suspensions, ointments and creams. Ointments usually contain lipophylic excipients such as mineral oil or vaseline. Solutions for ophthalmic use can contain sodium chloride, acid and/or base to adjust the pH, and purified water and preservatives.

**Please replace the paragraph beginning at page 9, line 20, with the following rewritten paragraph:**

The effective antiallergic or antihistaminic amount of polymorph 1 of bilastine for topical administration varies between 0.1 and 5% of the total weight of the pharmaceutical compound. The preferred amount ranges from 0.1 to 2% of the total weight of the pharmaceutical compound.

**Please replace the paragraph beginning at page 9, line 25, with the following rewritten paragraph:**

The effective antiallergic or antihistaminic amount of polymorph 1 of bilastine for oral administration varies from 1 to 50 mg/day, with preferably an amount corresponding to approximately 2 to 20 mg/day in a single or fractionated doses.

**Please replace the paragraph beginning at page 10, line 1, with the following rewritten paragraph:**

Polymorph 1 of bilastine has antihistaminic properties that have been demonstrated in experimental pharmacological models, such as preventing histamine-induced lethality in guinea-pig and antagonism against cutaneous capillary permeability induced by histamine in the rat.

**Please replace the paragraph beginning at page 10, line 9, with the following rewritten paragraph:**

**EXAMPLE 1**

**Preparation of polymorph 1 of bilastine**

Dissolve bilastine (see the US patent no. 53,877,187 in isopropyl alcohol heated to reflux for approximately 15-20 minutes under nitrogen while stirring. Cool the solution to 50°C over 6 hours and stop stirring. Let the solution cool to room temperature and stir again for three hours, filter and wash with cold isopropyl alcohol. Dry the solid residue in a vacuum ~~cabinet~~ oven at 35-40°C to constant weight.

**Please replace the paragraph beginning at page 10, line 18, with the following rewritten paragraph:**

**EXAMPLE 2**

**Preparation of polymorph 1 of bilastine**

Heat a suspension of bilastine (see US patent no. 5,877,187) in n-butanol and reflux for 3 hours under nitrogen while stirring. Leave the solution to cool while stirring, filter off the solid residue and dry it in a vacuum ~~chamber~~ oven at 35-40°C at constant weight.

**Please replace the paragraph beginning at page 10, line 25, with the following rewritten paragraph:**

**EXAMPLE 3**

**Preparation of polymorph 1 of bilastine**

Treat a mixture of polymorphs 2 and 3 of bilastine for several hours with hot acetone. Let the mixture cool to room temperature and filter off the solid residue. Dry it to constant weight.

**Please replace the paragraph beginning at page 11, line 1, with the following rewritten paragraph:**

**EXAMPLE 4**

**Preparation of polymorph 1 of bilastine**

Dissolve polymorph 3 of bilastine in isopropyl alcohol heated to reflux and stir for approximately 15-20 minutes under nitrogen. Let the solution reach room temperature

constantly stirring, filtering and washing with cold isopropanol. Dry the solid in a vacuum chamber oven at 35-40°C to constant weight.

**Please replace the paragraph beginning on page 11, line 10, with the following rewritten paragraph:**

#### **EXAMPLE 5**

##### **Preparation of polymorph 1 of bilastine**

Dissolve polymorph 2 of bilastine in n-butanol heated to reflux while stirring for approximately 3 hours. Let the solution reach room temperature while stirring, filtering and draining. Dry the solid in a vacuum chamber oven at 35-40°C to constant weight.

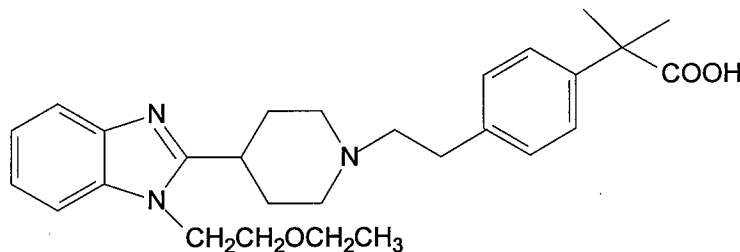
#### **In the Abstract:**

**Please amend the Abstract as follows –**

#### **ABSTRACT**

**Polymorph of 4-[2-[4-[1-(2-ethoxyethyl)-1H-benzimidazole benzimidazole-2-yl]-1-piperidinyl]ethyl]- $\alpha\alpha$ -dimethyl-benzenecarboxylic acid**

Polymorph of 4-[2-[4-[1-(2-ethoxyethyl)-1H-benzimidazole benzimidazole-2-yl]-1-piperidinyl]ethyl]- $\alpha\alpha$ -dimethyl-benzenecarboxylic acid of formula (I) is described, procedures for its preparation, pharmaceutical formulae containing polymorph 1 and the use of polymorph 1 to treat allergic reactions and pathological processes mediated by histamine in mammals such as man.



(I)